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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,247	02/11/2002	Gary L. Griffiths	018733-1093	9630

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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	7

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,247	GRIFFITHS, GARY L.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on th cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-12 and 16-20* is/are rejected.

7)☒ Claim(s) *13-15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 9-20 are pending.

2. In view of the amendment filed 12/23/03, the following rejections remain.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 9-12 and 16-20 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for detecting a tissue in a patient by a) administering to a patient a bispecific antibody or antibody binding fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to a specific F-18 labeled peptide such as the ones recited in claims 13-15 or a low molecular weight hapten conjugated to said F-18-labeled peptide and allowing the bispecific antibody or antibody fragment to bind to the target tissue and the non-targeted bispecific antibody or antibody fragment to clear, b) administering the F-18-labeled peptide such as the ones recited in claims 13-15 or the hapten conjugate thereof to the patient, and allowing said F-18 labeled peptide or the hapten conjugate thereof to bind to the bispecific antibody or the antibody fragment, and the unbound F-18-labeled peptide or hapten conjugate thereof to clear, and c) detecting the F-18-labeled peptide thereby detecting the target tissue by positron emission tomography, **does not** reasonably provide enablement for (1) a method for detecting a tissue comprising a) administering to a patient a bispecific antibody or antibody binding fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to *any* F-18-labeled peptide or any low molecular weight hapten conjugated to *any* F-18-labeled peptide and allowing the bispecific antibody or antibody fragment to bind to the target tissue and the non-targeted bispecific antibody or antibody fragment to clear, b) administering *any* F-18-labeled peptide or the hapten conjugate thereof to the patient, and allowing said F-18 labeled peptide or the hapten conjugate thereof to bind to *any* bispecific antibody or the antibody fragment, and the unbound F-18-labeled peptide or hapten conjugate thereof to clear, and c) detecting the F-18-labeled peptide thereby detecting the target tissue, (2) the said method wherein the F-18-labeled peptide contains a thiol group, (3)

the said method wherein the F-18-labeled peptide is labeled according to a method for radiolabeling a thiol-containing peptides with any fluorine-18 (F-18) comprising reacting any peptide comprising a free thiol group with a labeling reagent having the general formula 18F-(CH2)m-CR1R2-(CH2)n-X wherein n is 0, 1 or 2; m is 0, 1 or 2; and n+m is 0, 1 or 2; X is selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate, triflate, unsubstituted maleimide, maleimide substituted with one or two alkyl groups and 3-sulfo-maleimide and R1 and R2 are the same or different are selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate, triflate, hydrogen, CONH2, carboxyl, hydroxyl, sulfonic acid, tertiary amine, quaternary ammonium, unsubstituted alkyl, substituted alkyl, -COOR', -CONR'2 or COR' wherein the substituents of the substituted alkyl groups are selected from the group consisting of -CONH2, carboxyl, hydroxyl, sulfonic acid, tertiary amine and quaternary ammonium and wherein R' is C1-C6 alkyl or phenyl, or a method for radiolabeling thiol-containing peptides with fluorine-18 (F-18), comprising reacting any peptide comprising a free thiol group with a F-18 fluorinated alkene, wherein at least one of the two double-bonded carbon atoms bears at least one leaving group selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate ad triflate, (3) the said method wherein the hapten is any metal chelate complex, (4) the said method wherein the metal chelate complex comprises manganese, iron, or gadolinium, (5) the method mentioned above wherein the bispecific antibody or antibody fragment is *any* monoclonal *any* humanized antibody, (6) the method mentioned above wherein the F-18-labeled peptide is detected by positron emission tomography. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a method for detecting a tissue using a specific bispecific or humanized monoclonal antibody or Fab fragment thereof where one arm is specific for a target tissue of the patient and the other arm is specific for an F-18-labeled peptide selected from the group consisting of X-Gly-D-Tyr-D-Trp-Gly-D-Lys(X)-Gly-D-Tyr-DTrp-OH where X represents a free or protected amino acid group, Ac-Cys(Y)-D-Tyr-D-Trp-Gly-D-Cys(Y)-Gly-Dtyr-D-Trp-OH wherein Y represents a free or protected thiol group, and Ac-Gly-D-iodo-Tyr-Trp-Gly-D-Lys(Ac)-Gly-D-Trp-OH by positron emission tomography (PET).

The specification does not teach how to make and use *any* bispecific or humanized monoclonal antibody or Fab fragment thereof where one arm is specific for *any* target tissue of the patient and the other arm is specific for *any* F-18-labeled peptide, *any* low molecular weight hapten conjugated to *any* F-18-labeled peptide mentioned above for a method for PET imaging. There is insufficient guidance with regard to the binding specificity and affinity of any antibody for PET imaging. Further, there is no vivo working examples demonstrating that any antibody with unknown specificity would be useful for a method of detecting a tissue in a patient using PET. Other than the specific F-18 labeled peptides mentioned above, there is insufficient guidance about the structure (amino acid residues) of any of F-18 labeled peptide. Without the specific amino acid residues, one of skilled in the art cannot even contemplate of making such antibody that would have one arm specific for any F-18 labeled peptide and one arm would be specific for any tissue in a patient.

Kuby *et al* teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide.

Colman *et al* teach that even a single amino acid changes within the interface of an antibody-antigen can raise or lower the affinity of the antibody (See page 33, in particular).

Given the indefinite number of undisclosed antibody, F-18 labeled peptide, it is unpredictable which undisclosed antibody and undisclosed F-18 labeled peptide would be useful for a detection method. Since the F-18 labeled peptide is not enabled, it follows that *any* low molecular weight hapten conjugated to *any* undisclosed F-18 labeled peptide is not enabled. It also follows that the method of labeling any undisclosed peptide and any metal chelate complex to any undisclosed peptide are not enabled.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed 12/23/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the method of making antibodies to any immunogen is straightforward, (2) The bsMab, bsFab, and associated methodologies described in provisional application 60/090,142, which mentioned on page 4 of instant application are incorporated by reference.

In response to applicant's argument, although the method of making antibodies to any immunogen appears to be straightforward, the term "comprising" is open-ended. It expands the bispecific antibody or antibody fragment to include additional amino acids at either or both ends. Further, the "peptide" in the F-18-labeled peptide without SEQ ID No has no structure (no amino acid sequence). There is insufficient guidance as to the structure of the F-18-labeled peptide. Because the F-18-lebeled peptide is not enabled, it follows that any bispecific antibody or antibody fragment conjugated to the F-18-labeled peptide for a method of detecting a tissue of issue is not enabled. The specification discloses only a method for detecting a tissue using a specific bispecific or humanized monoclonal antibody or Fab fragment thereof where one arm is specific for a target tissue of the patient and the other arm is specific for F-18-labeled peptide selected from the group consisting of X-Gly-D-Tyr-D-Trp-Gly-D-Lys(X)-Gly-D-Tyr-DTrp-OH where X represents a free or protected amino acid group, Ac-Cys(Y)-D-Tyr-D-Trp-Gly-D-Cys(Y)-Gly-Dtyr-D-Trp-OH wherein Y represents a free or protected thiol group, and Ac-Gly-D-iodo-Tyr-Trp-Gly-D-Lys(Ac)-Gly-D-Trp-OH by positron emission tomography (PET). Given the indefinite number of undisclosed antibody, F-18 labeled peptide, it is unpredictable which undisclosed antibody and undisclosed F-18 labeled peptide would be useful for a detection method. Since the F-18 labeled peptide is not enabled, it follows that *any* low molecular weight

hapten conjugated to *any* undisclosed F-18 labeled peptide is not enabled. It also follows that the method of labeling any undisclosed peptide and any metal chelate complex to any undisclosed peptide are not enabled.

5. Claims 9-12 and 16-20 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method for detecting a tissue comprising a) administering to a patient a bispecific antibody or antibody binding fragment comprising an arm that is specific to a target tissue of the patient and another arm that is specific to *any* F-18-labelde peptide or any low molecular weight hapten conjugated to *any* F-18-labeled peptide and allowing the bispecific antibody or antibody fragment to bind to the target tissue and the non-targeted bispecific antibody or antibody fragment to clear, b) administering *any* F-18-labeled peptide or the hapten conjugate thereof to the patient, and allowing said F-18 labeled peptide or the hapten conjugate thereof to bind to *any* bispecific antibody or the antibody fragment, and the unbound F-18-labeled peptide or hapten conjugate thereof to clear, and c) detecting the F-18-labeled peptide thereby detecting the target tissue, (2) the said method wherein the F-18-labeled peptide contains a thiol group, (3) the said method wherein the F-18-labeled peptide is labeled according to a method for radiolabeling a thiol-containing peptides with any fluorine-18 (F-18) comprising reacting any peptide comprising a free thiol group with a labeling reagent having the general formula 18F-(CH2)m-CR1R2-(CH2)n-X wherein n is 0, 1 or 2; m is 0, 1 or 2; and n+m is 0, 1 or 2; X is selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate, triflate, unsubstituted maleimide, maleimide substituted with one or two alkyl groups and 3-sulfo-maleimide and R1 and R2 are the same or different are selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate, triflate, hydrogen, CONH2, carboxyl, hydroxyl, sulfonic acid, tertiary amine, quaternary ammonium, unsubstituted alkyl, substituted alkyl, -COOR', -CONR'2 or COR' wherein the substituents of the substituted alkyl groups are selected from the group consisting of -CONH2, carboxyl, hydroxyl, sulfonic acid, tertiary amine and quaternary ammonium and wherein R' is C1-C6 alkyl or phenyl, or a method for radiolabeling thiol-containing peptides with fluorine-18 (F-18), comprising reacting any peptide comprising a

free thiol group with a F-18 fluorinated alkene, wherein at least one of the two double-bonded carbon atoms bears at least one leaving group selected from the group consisting of iodide, bromide, chloride, azide, tosylate, mesylate, nosylate ad triflate, (3) the said method wherein the hapten is any metal chelate complex, (4) the said method wherein the metal chelate complex comprises manganese, iron, or gadolinium, (5) the method mentioned above wherein the bispecific antibody or antibody fragment is *any* monoclonal *any* humanized antibody, (6) the method mentioned above wherein the F-18-labeled peptide is detected by positron emission tomography.

The specification discloses only a method for detecting a tissue using a specific bispecific or humanized monoclonal antibody or Fab fragment thereof where one arm is specific for a target tissue of the patient and the other arm is specific for an F-18-labeled peptide selected from the group consisting of X-Gly-D-Tyr-D-Trp-Gly-D-Lys(X)-Gly-D-Tyr-DTrp-OH where X represents a free or protected amino acid group, Ac-Cys(Y)-D-Tyr-D-Trp-Gly-D-Cys(Y)-Gly-Dtyr-D-Trp-OH wherein Y represents a free or protected thiol group, and Ac-Gly-D-iodo-Tyr-Trp-Gly-D-Lys(Ac)-Gly-D-Trp-OH by positron emission tomography (PET).

With the exception of the specific F-18-labeled peptides mentioned above, there is insufficient written description about the structure associated with function of any F-18-labeled peptides, *any* low molecular weight hapten conjugated to *any* undisclosed F-18 labeled peptide and *any* bispecific monoclonal or humanized antibody or binding fragment thereof that is specific for *any* F-18-labeled peptide. Further, Applicants disclose only three F-18-labeled peptides, there is a lack of a written description of *any* additional F-18-labeled peptide, low molecular weight hapten conjugated F-18-labeled peptide and antibody that binds to any tissue and any F-18-labeled peptide for a method for detecting a tissue by positron emission tomography. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 12/23/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) for each claim drawn to a genus, as in claim 9, the written description requirement may be satisfied through sufficient description of a representative number of species by actual reduction to practice.

In response to applicant's argument, the specification discloses only three F-18-labeled peptide selected from the group consisting of X-Gly-D-Tyr-D-Trp-Gly-D-Lys(X)-Gly-D-Tyr-DTrp-OH where X represents a free or protected amino acid group, Ac-Cys(Y)-D-Tyr-D-Trp-Gly-D-Cys(Y)-Gly-Dtyr-D-Trp-OH wherein Y represents a free or protected thiol group, and Ac-Gly-D-iodo-Tyr-Trp-Gly-D-Lys(Ac)-Gly-D-Trp-OH by positron emission tomography (PET) for a method of detection. The claims are drawn to indefinite number of F-18-labeled peptide conjugated to any bispecific antibody or antibody fragment for a method for detecting the target tissue. Other than the specific F-18 labeled peptide mentioned above, there is insufficient written description about the structure associated with function of any "peptide" within the F18-labeled peptides because F-18-labeled peptide without amino acid sequence (SEQ ID NO) has no structure, let alone for a method of detecting the targeted tissue of interest in vivo. Given there are only three F-18-labeled peptides for the claimed method of detection, One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

6. Claims 13-15 stand objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

7. No claim is allowed.

8. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be

calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

10. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Phuong N. Huynh, Ph.D.
Patent Examiner
Technology Center 1600
March 10, 2003

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